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Progression of Asbestosis Predicts Lung Cancer*

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Study objectives: **To explore whether the progression of asbestosis correlates with the risk of lung cancer among patients with asbestosis.**

Design: **A group of 85 asbestosis patients (78 men and 7 women) were radiographically followed up between 1979 and 1987. Two or three posteroanterior radiographs taken from each patient in 1978 to 1979, 1983 to 1984, and 1986 to 1987 were classified according to the International Labour Office 1980 classification and were used to divide the patients into progressors and nonprogressors. Follow-up for cancer was done automatically through the files of the Finnish Cancer Registry from the time of determination of the progression status to December 31, 1994. Predictors of lung cancer risk were studied with a logistic regression model, and the standardized incidence ratio (SIR) was calculated for lung cancer.**

Results: **Of the 24 male patients with progressive small opacity profusion, 11 (46%) developed lung cancer, as opposed to 5 (9%) of the 54 male patients without progression. The SIR for lung cancer was 37 (95% confidence interval, 18 to 66) for the progressors and 4.3 (1.4 to 9.9) for the nonprogressors. In both groups, all the lung cancer cases occurred among smokers or ex-smokers. None of the seven female patients showed progressive small opacity profusion. One of them developed lung cancer. In the logistic regression model including all 85 asbestosis patients, radiographic progression of small opacity profusion (p=0.0009) and current smoking (0.0021) were significant predictors of lung cancer morbidity.**

Conclusions: **Asbestosis patients with radiographic progression of small opacity profusion over a few years are at a higher risk of lung cancer than those with a less aggressive course of the disease. The progression of pulmonary fibrosis may be an independent risk factor that, in addition to smoking history and the intensity of asbestos exposure, could be used to estimate lung cancer risk.** ***(CHEST 1998; 113:1517-21)***

Key words: asbestosis; cohort study; follow-up; ILO classification; incidence; lung cancer; record linkage; smoking

Abbreviations: CI=confidence interval; FIOH=Finnish Institute of Occupational Health; ILO=International Labour Office; SIR=standardized incidence ratio

Asbestos exposure increases the risk of lung cancer. Some studies have found that the increased risk occurs only if evidence of pulmonary fibrosis is present,[1,2] while others report that the risk is associated with exposure dose independently of fibrosis.[3,4] A relation has been observed between the severity of asbestosis and death from lung cancer.[5] One relationship that has yet to be established is whether the progression of pulmonary fibrosis among asbestosis patients correlates with lung cancer risk. This possible association was the focus of our present study.

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Materials and Methods

In Finland, the diagnosis for asbestosis during the 1970s was based on a history of confirmed occupational exposure to asbestos and radiographic findings consistent with asbestosis. The occurrence of small opacities large enough to receive a grade of 1/0 or higher according to the radiographic classification of the International Labour Office (ILO) was regarded as asbestosis. If, however, heavily exposed workers had restrictive lung function impairment, impairment of diffusion capacity or physical findings (rales/clubbing), asbestosis was diagnosed even if only minimal parenchymal findings (ILO small opacities grade <1/0) were

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present.[6] Periodic medical examinations of pneumoconiosis patients are included in the prevailing practices of occupational health surveillance in Finland, and this follow-up was organized by the Finnish Institute of Occupational Health (FIOH) as a part of such surveillance.

The study population consisted of 128 asbestosis patients who visited the FIOH from 1979 to 1987 for a periodic health examination because of previously diagnosed asbestosis or a diagnosis of asbestosis received from 1979 to 1985. No selection was made. Eighty-five of these patients visited the FIOH at least twice and thus could be followed up radiographically, and they comprise the present study group.

Two or three posteroanterior radiographs taken from each patient from 1978 to 1979, 1983 to 1984, and 1986 to 1987 were classified according to the 1980 ILO classification of radiographs of pneumoconioses.[7] The ILO classification offers a standard for classifying lung opacities and pleural abnormalities provoked by the inhalation of dusts. It is based on a set of standard radiographs and a classification guideline. In our study, the radiographs of each patient were examined in random order with the identification labels covered. Each radiograph was classified together by three readers (two radiologists, one being a certified National Institute of Occupational Safety and Health B-reader, and one physician with experience in ILO classification). If the classification differed, a joint decision was made. The complete classification with a 12-point scale for the profusion of small opacities was used. The major ILO categories 0 to 3 were used for the profusion of small opacities to divide the patients into "progressors" and "nonprogressors." Progression was accepted if the second or third radiograph was classified into a higher major ILO category than the first. In the statistical analyses, progression was also defined as a change of at least two minor ILO categories (*eg*, from 1/0 to 1/2). As the results were similar, only the results of the analyses using the first definition are shown. The mean interval between the radiographs used in the assessment of progression was 4 (range, 2 to 9) years. None of the radiographs aroused any suspicion of pulmonary malignancy. The radiographs were classified before the follow-up for cancer.

The demographic and exposure data of the patients are given in Table 1. The mean interval between the diagnosis of asbestosis and the beginning of the follow-up for the radiographic progression of asbestosis was 5 years and the start of the follow-up for cancer was 9 years.

The subjects were identified and followed up for death and emigration up to 1994 in the Population Register Center through the use of the unique personal identification number given to everyone residing in Finland since 1967. The follow-up for cancer was done automatically through the files of the Finnish Cancer Registry. It started on January 1 of the year following the year of the last radiograph used in the determination of progression status. The calculation of person-years ended at emigration, death, diagnosis of lung cancer, or on December 31, 1994, whichever occurred first. The number of cancer cases and the person-years at risk were counted according to 5-year age groups, separately for 1981 to 1987 and 1988 to 1994. There were only seven women in the study population, and therefore the cancer risk was estimated for the men only. The expected number of cases of lung cancer was calculated by multiplying the number of person-years in each age group by the corresponding average lung cancer incidence in Finland during the period of observation. The standardized incidence ratio (SIR) was calculated by dividing the observed number of cases by the expected number of cases. The 95% confidence interval (CI) for the SIR was calculated on the presumption that the number of observed cases followed a Poisson distribution.

The statistical analyses were carried out using statistical software (SPSS for Windows, Release 6.1; Chicago). A forward stepwise logistic regression model was used to determine the statistical significance of the predictors associated with lung cancer. The following possible predictors were included in the model: progression in the profusion score of small opacities (yes/no), age at the beginning of the radiographic follow-up, occupation (asbestos-sprayer/other), exposure time (years in the occupation), smoking, minor ILO category at the beginning of the follow-up, and time lag between the diagnosis of asbestosis and the beginning of follow-up. The categorical variant smoking was divided into ever-smokers (yes/no) and current smokers (yes/no).

Table 1—*Demographic Data of Patients With and Without Radiographic Progression of Asbestosis*

Characteristic	Asbestosis Patients	
	With Progression	Without Progression
Male/female, No.	24/0	54/7
Years of age at beginning of follow-up, mean (range)	49 (32-63)	54 (34-70)
Years of exposure, mean (range)	19 (4-30)	20 (4-40)
Years of follow-up for cancer, mean (range)	5.7 (1-10)	8.3 (1-11)*
Smoking habits		
Nonsmokers, No. (%)	3 (13)	12 (20)
Smokers, No. (%)	10 (42)	20 (33)
Ex-smokers, No. (%)	11 (46)	29 (48)
Years of smoking among current and ex-smokers at start of radiographic follow-up, mean (range)	26 (9-43)	24 (5-44)
Occupation		
Insulator, No. (%)	6 (25)	23 (38)
Asbestos quarry worker, No. (%)	5 (21)	15 (25)
Asbestos product factory worker, No. (%)	2 (8)	15 (25)
Asbestos sprayer, No. (%)	7 (29)	4 (7)*
Other, No. (%)	4 (17)	4 (7)

*Statistically significant difference between the patient groups, $p<0.05$.

Results

Of the 24 male patients with progression according to the ILO score, 11 (46%) developed lung cancer, as opposed to 5 (9%) of the 54 male patients without progression. All the female patients were nonprogressors, and one of them developed lung cancer (Table 2). In both groups, all the lung cancer cases were detected in smokers or ex-smokers; 80% of the current smokers and 30% of the ex-smokers with progressive asbestosis developed lung cancer. The corresponding figures for patients with nonprogressing fibrosis were 20% and 7%, respectively. The mean delay between the diagnosis of asbestosis and the diagnosis of lung cancer was 14 (range, 7 to 22) years for the progressors and 18 (range, 8 to 26) years for the nonprogressors.

At the start of the radiographic follow-up for small

Table 2—*Asbestosis Patients With and Without Radiographic Evidence of Asbestosis Progression by Cancer Status*

Change of ILO Group	Lung Cancer	Other Cancer*	No Cancer	Total No. (%)
Progressors				
0→1,2	1	—	3	4 (17)
1→2,3	9	4	5	18 (75)
2→3	1	—	1	2 (8)
Total	11	4	9	24 (100)
Nonprogressors				
0→0	1	—	8	9 (15)
1→1	4	5	35	44 (72)
2,3→2,3	1	—	7	8 (13)
Total	6	5	50	61 (100)

*Other cancers among the progressors: rectal cancer, pancreatic cancer, cancer of the thyroid gland, and lymphoma; other cancers among the nonprogressors: mesothelioma (two cases), pancreatic cancer, stomach cancer, and cancer of the uterine cervix.

opacity progression, 13 patients were in the major ILO category 0. During the cancer follow-up, two of them (15%) developed lung cancer. Similarily, 13 of the 62 (21%) in ILO category 1 and 2 of the 10 (20%) in ILO category 2 at the beginning of the study developed lung cancer. There were no significant differences in the ILO categories of the progressors and nonprogressors at the beginning of the study, 72% of the nonprogressors and 75% of the progressors being classified into ILO category 1 (Table 2).

According to the forward stepwise logistic regression model, only small opacity progression and current smoking were statistically significant predictors of lung cancer (Table 3). Smoking was not a significant predictor of small opacity progression.

Among the male patients, the SIR for lung cancer was 37 for the progressors and 4.3 for the nonprogressors (Table 4).

Discussion

Our results show that asbestosis patients with radiographic progression over a few years have a higher risk of lung cancer than those with a less aggressive course of the disease. The observed risk for lung cancer is high for our asbestosis patients (SIR=11) in comparison to that of asbestos-exposed cohorts, including both patients with and those without asbestosis. It corresponds, however, to the sixfold risk observed in an international meta-analysis of asbestosis cohorts,[8] to the sevenfold risk for all notified Finnish asbestosis patients,[9] and to the 10-fold risk observed in a cohort of Finnish asbestosis patients.[10] About 50% of our patients whose asbestosis showed progression, and about 10% of those without progression received a diagnosis of lung cancer during the follow-up. The proportions were even higher if only smokers were considered. In the follow-up of 17,800 North American insulation workers, about 25% of deaths were due to lung cancer.[11] The proportion of lung cancer deaths in that cohort, however, was not reported separately for patients with radiographic asbestosis, or according to smoking status, and thus it cannot be compared directly with that of our patients.

All of our patients had been heavily exposed to asbestos, although the intensity of direct or indirect occupational exposure varied. The duration and type of exposure, however, were similar for the patients with progressive small opacity profusion and those without such progression. Differences in the intensity or type of asbestos exposure are thus unlikely to explain the 10-fold difference in the risk of lung cancer between those with and those without progressive asbestosis.

It has been reasonably well established that smoking correlates with the ILO small opacity score among patients with asbestosis.[12-14] If the progressor status were to correlate with the intensity of smoking, our results would be explained at least partly by differences in smoking. There were slightly more current smokers among the progressors than among the nonprogressors (42% vs 33%). The difference in the occurrence of lung cancer between the progressors and the nonprogressors, however, was observed among both current smokers and ex-smokers. In the logistic regression analysis, smoking was not a significant predictor of the progression of small opacity profusion. The progression of asbestosis was a significant predictor of lung cancer when smoking was included in the statistical model. Even though we could not adjust for the amount of smoking, it seems unlikely

Table 3—*Odds Ratios Derived From the Best-fitting Stepwise Logistic Regression Model for the Predictors Associated With Lung Cancer Among the Asbestosis Patients**

Variable	OR (95% CI)
Progression of small opacities (Yes vs no)	9.6 (2.53-36.8)
Current smoker (Yes vs nonsmoker/ex-smoker)	8.3 (2.15-32.2)

*The other variables included in the model (but found not to improve the fit significantly) were as follows: ever-smoker (yes/no), age (years) at the beginning of the radiographic follow-up, occupation (asbestos-sprayer/other), exposure time (years in the occupation), ILO minor category at the beginning of the follow-up, and time lag between the diagnosis of asbestosis and the beginning of the follow-up. OR=odds ratio.

Table 4—*Observed Numbers of Lung Cancer Cases and the SIRs With the 95% Confidence Intervals for the Male Asbestosis Patients by Progression Category

Study Group	Person-Years	Obs	SIR	95% CI
All	582	16	11	6.2-18
Progressors	136	11	37	18-66
Nonprogressors	446	5	4.3	1.4-9.9

*Obs=observed numbers of lung cancer cases.

that differences in the intensity of smoking would explain the observed association between the progression of asbestosis and the risk of lung cancer.

Small opacity assessment according to the ILO classification is subject to interobserver and intraobserver variation.[15] The effect of this variation was reduced by using only the major categories 0, 1, 2, and 3 and a consensus-based classification. It is noteworthy that none of the patients had their last radiograph classified into a lower major or minor category than the first. By definition, all cases classified into the major ILO category of 3 in the first radiograph were classified as nonprogressors because category 3 is the highest classification possible. As patients with severe fibrosis may have had a higher risk of lung cancer, the effect of such a classification "bias" would be to reduce the observed difference between the progressors and nonprogressors.

As we studied only patients with asbestosis, the results do not contribute to the scientific discussion on the association between asbestos and lung cancer in the absence of fibrosis. The carcinogenic processes of asbestos, tobacco smoke, and their interaction are probably complex, and both direct fiber effects and effects mediated through fibrosis may exist.[1,4] At the cellular level, the processes of asbestos-related inflammation, fibrosis, and carcinogenesis seem to be at least somewhat connected.[16] Our results suggest that the progression of pulmonary fibrosis may be an independent risk factor that, in addition to smoking history and the intensity of asbestos exposure, could be used to estimate lung cancer risk. The association between the risk of lung cancer and the progression of fibrosis may be due at least partly to a common individual susceptibility factor. Genetic factors like glutathione S-transferase and N-acetyltranseferase genotype seem to be related to both nonmalignant and malignant asbestos-related disorders.[17]

Our results were obtained from a small cohort of heavily exposed asbestosis patients. The progression status was determined several years after the diagnosis of asbestosis, and the lung cancer cases were typically diagnosed >10 years after the diagnosis of asbestosis. Those with progressive asbestosis had probably had a progressive course of disease already before the beginning of the radiographic follow-up. The fact that those showing asbestosis progression were on the average 5 years younger than those without progression (Table 1) may indicate that they had had a more rapid course of the disease even before the start of the radiographic follow-up. Yet the ILO category at entry into the radiographic follow-up was similar for the patients with and those without progression (Table 2), and the ILO category at entry was not a significant predictor of lung cancer risk in the logistic regression analyses.

Further studies are needed to confirm the possible independent role of asbestosis progression in the asbestos-associated risk of lung cancer. Such studies should also address the time factors involved in the progression of fibrosis and the occurrence of lung cancer. The extremely high incidence of lung cancer among smokers with progressive asbestosis should be taken into account when screening or other secondary prevention activities or studies are planned.

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